IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: HADLACZKY *et al.*

Serial No.:09/096,648
Confirmation No: 2049

Filed: June 12, 1998

For: ARTIFICIAL CHROMOSOMES, USES THEREOF AND METHODS FOR PREPARING ARTIFICIAL CHROMOSOMES

Group Art Unit: 1632

Examiner: Ton, Thaian N.

I hereby certify that this paper and the attached papers are being deposited with the United States Postal Service as first class mail in an envelope addressed to: Commissioner for Patents, Washington, D.C. 20231, on this date.

02/26/02
Date

Paula K. Schoeneck
Paula K. Schoeneck

AMENDMENT AFTER FINAL

Commissioner for Patents
Washington, D.C. 20231

Dear Sir:

Responsive to the Final Office Action mailed November 26, 2001 (the "Office Action"), consideration of the following remarks and entry of the following amendment, which is provided in accord with requirements set forth by the Examiner, are respectfully requested. It is respectfully submitted that entry of the amendment places the application into condition for allowance, or, alternatively, reduces the number of issues for appeal by obviating the grounds for rejection under 35 U.S.C. §112, first and second paragraphs, and complying with specific requirements set forth by the Examiner.

IN THE CLAIMS:

Please replace claims 33, 82 and 88 with amended claims 33, 82 and 88 as follows:

33. The method of claim 32, wherein the cell is a mouse embryonic stem cell.

82. A method of producing a non-human transgenic embryo, comprising:

introducing a satellite artificial chromosome into a cell; and

culturing the cell under conditions whereby it develops into a non-human embryo.

88. A method of producing a non-human transgenic embryo, comprising introducing a satellite artificial chromosome into a non-human embryo.

REMARKS

Any fees that may be due in connection with filing this paper or with this application during its entire pendency may be charged to Deposit Account No. 50-1213.

Claims 32-39, 43, 44, 59, 60, 65, 67, 71-74, 82-89 and 93-100 are presently pending in this application. Claims 33, 82 and 88 have been amended. The amendments to claims 33, 82 and 88 find basis in the specification and claims as originally filed. Therefore, since the amendments change the form, not the substance of the claimed subject matter, no new matter has been added. Accordingly, entry of the amendments to the claims is respectfully requested.

A marked up copy per 37 C.F.R. §1.121 of the amended claims is attached to this response.

CLAIMS DEEMED ALLOWABLE:

Claims 98 and 99

It is stated on page 2 of the Office Action that the Perez Declaration (Paper No. 17) is sufficient with regard to the following enabled scope: "a method for producing a transgenic non-human mammal comprising introducing in a female non-human mammal an ovum comprising a SATAC, wherein the ovum develops into a zygote or embryo; and allowing the embryo to develop

into a transgenic non-human mammal comprising said SATAC; and a method for producing a transgenic mouse comprising introducing mouse embryonic stem cells comprising a SATAC into a mouse embryo and introducing said embryo into a female mouse; and allowing the embryo to develop in to a transgenic mouse comprising said SATAC." It is further stated on page 5 of the Office Action that claims 98 and 99 appear to be allowable. Accordingly, it appears that claims 98 and 99 are deemed in the Office Action to be commensurate with the enabled scope as set forth in the Office Action.

Claims 98 and 99 are directed to methods for producing a transgenic non-human mammal by introducing a fertilized oocyte containing a satellite artificial chromosome or mouse embryonic stem cell containing a satellite artificial chromosome within an embryo into a female non-human mammal and allowing the embryo to develop into a transgenic mammal. These claims thus specify that the cell containing the satellite artificial chromosome is a fertilized oocyte or mouse embryonic stem cell which are asserted in the Office Action to be sufficient for development into an animal.

Additional Claims Specifying a Fertilized Cell or Mouse Embryonic Stem Cell

Although claims 98 and 99 are deemed allowable in the Office Action, the remainder of the pending claims are rejected because they allegedly are "missing critical steps dependent on the source cells" (see below for a more detailed discussion of the rejection and the specific rebuttal of the rejection). It is respectfully submitted, however, that there are claims pending (i.e., claims 33, 34, 38, 39, 65, 71, 85-89 and 97) in addition to claims 98 and 99 which specify that the cell containing an artificial chromosome is a fertilized ovum, zygote, embryo or mouse embryonic stem cell and that are not within the purview of the rejection. For example, claims 33, 65, 71 and 87 specify that the cell comprising an artificial chromosome is either a fertilized ovum or a mouse embryonic stem cell, which are cells identified in the Office Action as sufficient for development into an animal.

Claims 34, 88, 89 and 97 specify that the cell containing an artificial chromosome is in an embryo or that an embryo containing an artificial chromosome is introduced into a female non-human animal. An embryo is identified in the Office Action as a composition that can develop into an animal. Furthermore, it is noted that in the specific discussion of the claim rejections on pages 2-6 of the Office Action, independent claims 88 and 97 are **not** recited as being included among the rejected claims.

Claim 39 specifies that the cell containing an artificial chromosome is a zygote. A zygote is known in the art as a cell produced by union of a male and female gamete, i.e., a cell resulting from fertilization (see, *e.g.*, the definition of a "zygote" in *Websters II New College Dictionary*, 1995, Houghton Mifflin Co., Boston, a copy of which is provided herewith). Accordingly, a zygote appears to be of the type, i.e., a fertilized cell, identified in the Office Action as sufficient for development into an animal.

Claims 38, 85 and 86 specify that the artificial chromosome is contained in a pronucleus. A pronucleus is one of two haploid pronuclei (one from a female gamete and one from a male gamete) present following union of a male and female gamete (*e.g.*, sperm and egg) in fertilization and prior to fusion of the nuclei to yield a single diploid nucleus (see, *e.g.*, the definition of a "zygote" in *Websters II New College Dictionary*, 1995, Houghton Mifflin Co., Boston, a copy of which is provided herewith). Accordingly, a cell containing a pronucleus appears to be of the type, i.e., a fertilized cell, identified in the Office Action as sufficient for development into an animal.

Because claims 33, 34, 38, 39, 65, 71, 85-89 and 97 recite cells or embryos which are compositions that are identified in the Office Action as sufficient for development into an animal, and there is no other basis on which the claims are rejected (with the exception of claims 33 and 85-89, additional rejections of which are addressed below), allowance of the claims is respectfully requested.

THE REJECTION OF CLAIMS 32-39, 43, 44, 59, 60, 65, 67, 71-74, 82-89, 93-97 and 100 UNDER 35 U.S.C. §112, FIRST PARAGRAPH

Claims 32-39, 43, 44, 59, 60, 65, 67, 71-74, 82-89, 93-97 and 100 stand rejected by the office action under §112, first paragraph, for the reasons advanced on pages 2-5 of the prior Office Action (mailed 3/1/01, Paper No. 18). Specifically, it is alleged that claims 32, 43, 44, 73, 82, 93, 95 and 96, which recite the term "cell(s)" and dependent claims that further distinguish the particular "cell(s)" are incomplete because they are missing critical steps dependent upon the source cells. As an example, the Office Action refers to a cell that is an unfertilized oocyte or germ cell which allegedly are not sufficient for development of any animal since they are not a fertilized ovum.

As discussed above, claims 33, 34, 38, 39, 65, 71, 85-89 and 97 are directed to methods of producing a transgenic non-human mammal or transgenic non-human embryo that include cells or embryos that are compositions that are identified in the Office Action as sufficient for development into an animal and therefore do not appear to be within the purview of this rejection.

The remaining claims, which do not specify a cell type or that recite a cell type other than a fertilized cell or a mouse embryonic stem cell, are as follows. Claims 32, 35, 43, 44, 59, 60, 67, 72-74, 82, 93-96 and 100 are directed to methods of producing a transgenic non-human mammal or a transgenic non-human embryo that include a step of introducing a cell containing an artificial chromosome into a female non-human mammal or a step of culturing a cell containing an artificial chromosome under conditions whereby it develops into a non-human embryo. Claims 36, 83, 84 are dependent on claim 32 or 82 and specify that the cell is an oocyte. Claim 37 is dependent on claim 32 and specifies that the cell is a germline cell. The rejection of these claims as incomplete because they are missing critical steps dependent on the source cells is respectfully traversed. Reconsideration of these grounds for the rejection is respectfully requested.

The claims are complete without recitation of fertilization or a fertilized cell

As described in the response (mailed September 4, 2001) to the previous Office Action, a variety of cells may be used in the claimed methods. Exemplary cells for use in the claimed methods are referred to in the application. In addition, in considering the teachings of the specification in combination with transgenic animal production methods known in the art at the time of filing of the instant application, it is clear that one of skill in the art could readily determine a number of cells that may be used in the claimed methods. For example, nuclear transfer methods for generating transgenic animals were known at the time of filing of the instant application [see, *e.g.*, Campbell *et al.* (1996) *Nature 380*:64-66 and PCT Application Publication No. WO95/17500].

Fertilization is not required for production of a transgenic animal

In nuclear transfer methods, a donor nucleus, which may contain heterologous nucleic acid, such as a transgene, is transferred into an enucleated oocyte which is then transferred into a recipient female for development into a transgenic animal. Thus, in these methods, an unfertilized oocyte does in fact develop into an animal, contrary to the assertion in the Office Action that such a cell will not develop into an animal. It is respectfully submitted, therefore, that fertilization is not essential to the claimed methods, and the pending method claims that recite "cell(s)" or that specify a cell that is not a fertilized cell are thus not missing critical steps depending upon the source cells but instead are complete as written.

It is noted in the Office Action that the Examiner did not consider the publications [Campbell *et al.* (1996) *Nature 380*:64-66 and PCT Application Publication No. WO95/17500] referred to in the previous response as evidence that nuclear transfer methods for generating transgenic animals were known at the time of filing of the instant application because copies of the publications

were not provided. Copies of the references are provided with this Response for consideration by the Examiner.

It is further asserted in the Office Action that while the specification broadly discusses the generation of transgenic animals by methods such as microinjection, the specification does not contemplate the use of nuclear transfer methods to generate the transgenic animals of the claimed invention. It is respectfully submitted that whether or not the specification provides an explicit recitation of nuclear transfer is not relevant to the issue of the completeness of the rejected claims. Patent documents need not include subject matter that is known in the field of the invention and is in the prior art, for patents are written for persons experienced in the field of the invention. See *Paperless Accounting, Inc. v. Bay Area Rapid Transit Sys.* 804 F.2d 659, 231 USPQ 649 (Fed. Cir. 1986) ("A patent applicant need not include in the specification that which is already known to and available to the public"). As described in the instant specification, the artificial chromosomes as provided therein are convenient and useful vectors for the introduction of heterologous genes into hosts and may be used in any methods that conventional vectors are used. The specification provides numerous examples of the use of the artificial chromosomes as vectors in a variety of methods, including the generation of transgenic animals. The Declaration of Perez under 37 C.F.R. §1.132 (mailed January 29, 2001) further demonstrates the use of the artificial chromosomes in the generation of transgenic embryos and animals as described in the application. There is no requirement for a patent application to provide a specific example of every possible embodiment of a claimed method. See *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991) ("It is well settled that patent applicants are not required to disclose every species encompassed by their claims, even in an unpredictable art..."). Instead, a patent application is deemed to include all that was known to those of skill in the art at the time of filing, and thus it is not necessary for the instant application to explicitly

reference all methods for generating transgenic animals known in the art at the time of filing.

Furthermore, whether or not nuclear transfer is explicitly referred to in the instant application, the fact remains that nuclear transfer is a method known to those of skill in the art at the time of filing of the application for generating transgenic animals that **does not require the use of a fertilized ovum.** As such, the Applicant has provided specific scientific evidence that clearly refutes the main basis of the grounds for rejection of the claims as set forth in the Office Action. The Office Action maintains that any cell that is not a fertilized ovum will not develop into an animal, and that assertion, which underlies almost all of the claim rejections, is simply not correct. It is therefore respectfully submitted that the rejection of claims on this basis cannot validly be maintained.

Transgenic embryos and animals can be produced using satellite artificial chromosomes whether or not the presence of such chromosomes constitutes "correct ploidy"

It is also alleged in the Office Action that "nuclear transfer methods require the correct chromosomal number or ploidy, which would not be present if a SATAC was present." It is respectfully submitted that addressing such an assertion is complicated by several factors. First, it is not clear what is meant by "correct" ploidy. Second, not only is this alleged requirement of nuclear transfer methods asserted without reference to acceptable published scientific evidence, it is set forth without *any* evidence or technical reasoning at all. Because the Applicant is unaware of this asserted requirement specifically for nuclear transfer methods and no reasoning is provided in support of the assertion, it is not possible to directly address any particular aspects of nuclear transfer that are being referred to by the Examiner.

Nonetheless, assuming, *arguendo*, that the condition the Examiner asserts, i.e., a lack of "correct ploidy" would occur in a cell if a satellite artificial chromosome is present in the cell, it is a condition that would occur irrespective

of the method used in the production of a transgenic animal. Such a condition would occur if transgenesis is carried out via pronuclear injection, delivery of embryonic stem cells, nuclear transfer or any other method. As described in the instant application and further demonstrated by the Declaration of Perez (Paper No. 17), satellite artificial chromosomes can be used and have been used as vectors in the development of transgenic embryos and animals comprising such chromosomes. The current Examiner and the previous Examiner have repeatedly recognized that the Perez Declaration is enabling for the development of a transgenic mouse. Accordingly, reconsideration of all the evidence and remarks provided herein and in previous Responses and Declarations under 37 C.F.R. §1.132 is respectfully requested as is withdrawal of the rejections made in the Office Action.

A possibility that not *every* cell used in a method of transgenic embryo or animal production would yield an embryo or animal is irrelevant to the scope of enablement of the claims

Furthermore, even if there is a possibility that not **every** cell would yield an embryo or animal in a method of transgenic animal production, it would not invalidate a claim that does not specify a particular cell type. *In re Dinh-Nguyen*, 492 F.2d 856 at 858-9, 181 USPQ 46,48 (CCPA (1974)). A claim is not too broad because it does not explicitly exclude possible inoperative applications of a method providing it enables one of skill in the art to practice what is claimed in its workable applications. Thus, what is relevant to the scope of enablement is that there are a number of cells, some of which are explicitly listed in the application and others that would be known to those of skill in the art based on the combination of the teachings of the application and what was known in the art at the time of filing of the application, that will develop into an embryo and a mammal. Therefore, the claims need not specify cell type in order to be enabled and definite.

It is respectfully submitted, therefore, that fertilization is not essential to the claimed methods, and the pending method claims that recite "cell(s)" or that do not specify that a particular cell is a fertilized cell are not missing critical steps depending upon the source cells but instead are complete as written.

Rejection of Claims Specifying Embryonic Stem Cells

With respect to claims that refer to "embryonic stem cells" without specifying "mouse," it is asserted in the Office Action that the art-recognized embryonic stem cell contributes to the germ line of an animal, and only embryonic stem cells isolated from the mouse have been established in the art at the effective filing date. It is further asserted that claim 33 recites the phrase mouse stem cell, however not all mouse stem cells would develop into a transgenic mouse and that only mouse embryonic stem cells would be capable of development into such an animal. In response, it is noted that all claims reciting "stem cell," *e.g.*, claims 33, 71, 87 and 99 (deemed allowable), to specify "mouse" stem cell. With respect to claim 33, in the interest of advancing prosecution, the claim has been amended to specify mouse "embryonic" stem cell, thereby rendering moot any such rejection.

Rejection of Claims Directed to Methods of Producing Transgenic Embryos

Claims 82-89, are rejected on the grounds that they are only enabled for a method of producing a transgenic non-human embryo. In the interest of advancing prosecution of the application the claims have been amended to specify "non-human."

THE REJECTION OF CLAIMS 32-39,43, 44, 59, 60, 65, 67, 71-74, 82-89, 93-96, and 100 UNDER 35 U.S.C. §112, SECOND PARAGRAPH

Claims 32-39, 43, 44, 59, 60, 65, 67, 71-74 and 82-89, 93-96 and 100 directed to a method of producing a transgenic animal or embryo are rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant

regards as the invention. Specifically, it is alleged in the Office Action that the claims are incomplete because they are missing critical steps depending upon the source cells. The Office Action directs applicant's attention to the "scope of enablement above." Thus, it appears that the same rejection of the claims is being made under 35 U.S.C. §112, first paragraph, as under 35 U.S.C. §112, second paragraph.

For the reasons provided above with respect to the rejection of the method claims on the same basis under 35 U.S.C. §112, first paragraph, it is respectfully submitted that all of the essential steps of the claimed methods are provided in the claims as pending. Accordingly, the rejection of the claims as indefinite due to a lack of completeness is respectfully traversed.

* * *

In view of the above amendments and remarks, reconsideration and allowance of the application are respectfully requested.

Respectfully submitted,
HELLER EHRMAN WHITE & McAULIFFE LLP

By: Paula K. Schoeneck
Paula K. Schoeneck
Registration No. 39,362

Attorney Docket No. 24601-402A
Address all correspondence to:
Stephanie Seidman
Heller Ehrman White & McAuliffe LLP
4350 La Jolla Village Drive
San Diego, California 92122-1246
Telephone: 858/450-8400

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Hadlaczky *et al.*

Serial No.: 09/096,648

Filed: June 12, 1998

For: *ARTIFICIAL CHROMOSOMES, USES THEREOF AND METHODS FOR PREPARING ARTIFICIAL CHROMOSOMES*

Art Unit: 1632

Examiner: Ton, Thaian N.

I hereby certify that this paper and the attached papers are being deposited with the United States Postal Service as first class mail in an envelope addressed to:
Commissioner for Patents
Washington, D.C. 20231, on this date.

02/26/02
Date

Paula Schoeneck
Paula Schoeneck

MARKED UP CLAIMS (37 C.F.R. § 1.121)

Please amend claims 33, 82 and 89 as follows:

33. (Thrice Amended) The method of claim 32, wherein the cell is a mouse embryonic stem cell.

82. (Amended) A method of producing a non-human transgenic embryo, comprising:

introducing a satellite artificial chromosome into a cell; and

culturing the cell under conditions whereby it develops into [an] a non-human embryo.

88. A method of producing [an] a non-human transgenic embryo, comprising introducing a satellite artificial chromosome into [an] a non-human embryo.